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REVIEW

Kounis syndrome☆

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Abstract Kounis syndrome (KS) was described in 1991 by Kounis and Zavras as the coincidental occurrence of acute coronary syndromes (ACSs) with allergic reactions (anaphylactic or anaphylactoid).

Today, allergic angina and allergic myocardial infarction are referred to as KS, and the latter has been reported in association with a variety of drugs, insect stings, food, environmental exposures and medical conditions, among other factors.

The incidence is not known, as most of the available information comes from case reports or small case series. In this article, the clinical aspects, diagnosis, pathogenesis, related conditions and therapeutic management of the syndrome are discussed.

PALABRAS CLAVE
Kounis;
Infarto de miocardio alérgico;
Angina alérgica

Síndrome de Kounis

Resumen El síndrome de Kounis (SK) fue descrito en 1991 por Kounis y Zavras como la aparición simultánea de eventos coronarios agudos y reacciones alérgicas anafilácticas o anafilactoides. Engloba conceptos como el de angina alérgica e infarto alérgico y se ha descrito en relación con picaduras de insectos, ingesta de fármacos y alimentos, exposiciones ambientales y condiciones médicas varias. Se desconoce su incidencia real ya que, la mayoría de lainformación proviene de casos clínicos o pequeñas series.

En el presente artículo se exponen los aspectos clínicos, diagnósticos, fisiopatología y tratamiento de este síndrome.

Introduction

KS was first described in 1991 by Kounis and Zavras as the simultaneous appearance of acute coronary events and anaphylactic or anaphylactoid allergic reactions.[1]

In an editorial published in 1998, Braunwald described that vasospastic angina could be induced by allergic reactions, with mediators such as histamine and leukotrienes acting upon the smooth muscle of the coronary arteries.[2]

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In this context, allergic angina and allergic acute infarction have been recognized as KS.[3] Even today the syndrome is little known, and most of the available information comes from the description of clinical cases (almost 300 in the literature to date)–mostly corresponding to adults, with some isolated pediatric cases.[4] Multiple causes have been described, including drugs, insect stings, foods, environmental exposures and medical conditions, among others.[5,6]

Recent data from the ARIAM study[7] indicate that acute myocardial infarction with transient ST-segment elevation, which probably would include most cases of KS, accounts for 4.6% of all cases of ACS admitted to the Intensive Care Unit (ICU), though only a very small proportion of cases would have KS as the underlying cause.

Classification

KS has been divided into two subtypes[8]:

- Type I (without coronary disease): chest pain during an acute allergic reaction in patients without risk factors or coronary lesions, in which the allergic event induces coronary spasm that causes chest pain and electrocardiographic changes secondary to ischemia, while the cardiac enzymes may be either normal or reflect progression towards acute myocardial infarction. The explanation for this type would be endothelial dysfunction and/or microvascular angina.
- Type II (with coronary disease): chest pain during an acute allergic reaction in patients with pre-existing atheroma disease (whether known or otherwise). Acute mediator release in such cases may induce atheroma plaque erosion or rupture, clinically resulting in acute myocardial infarction.

In recent years a third type has been proposed comprising patients with drug-eluting stent thrombosis,[9] where Giemsa and hematoxylin–eosin staining reveals the presence of mast cells and eosinophils, respectively.[10]

To date, three conditions have been related to KS:

- Takotsubo myocardiopathy[11] (stress-induced myocardiopathy affecting the left ventricle, producing hyperkinesia of the ventricle base and hypokinesia of the apex and midzone). These alterations would be caused by the action of inflammatory mediators in the same way as in KS.
- Coronary vascular disease in allogenic heart transplantation.
- Hypersensitivity myocarditis. In both cases there is an allergic cause–affecting the coronaries in the case of KS and the heart muscle and conduction system in the case of myocardiopathy. Clinically the two conditions may be indistinguishable–the differential diagnosis requiring magnetic resonance imaging (MRI) and in some cases cardiac biopsy.[12]

Etiology

A number of agents can give rise to KS, as reflected in Table 1.

In the case of insect stings and bites (bees and wasps), the venom contains proteins, peptides and vasoactive amines that can cause direct cardiotoxicity but also behave as allergens, with activation of the mast cells.[13]

In theory, any drug is able to trigger an allergic reaction, and thus potentially may cause KS. In practice, the drug substances most often associated with the syndrome are betalactams, nonsteroidal antiinflammatory drugs (NSAIDs), general anesthetics and iodine contrast media.[14–16]

Foods (shellfish and kiwi), latex, and snake venom are other potential causes.

As regards the related diseases, mention must be made of mastocytosis, characterized by clonal mast cell proliferation and clinically associated to repeated anaphylactic episodes. The patients show high serum tryptase levels outside the anaphylactic episodes, and the definitive diagnosis is based on the bone marrow biopsy findings.

Foreign bodies can also cause allergic reactions and KS, including conventional or drug-eluting stents.[17,18] In a recent review, Chen et al.[10] found patients with epicutaneous or patch tests positive for the metal components of the stents (nickel and molybdenum) to have a greater tendency to suffer stent thrombosis than those without such positive tests. On the other hand, new coronary events following drug-eluting stent placement may represent not only a local phenomenon but also a generalized hypersensitivity reaction including the release of mediators capable of inducing thrombotic and/or vasoconstrictive phenomena. The literature describes cases of severe diffuse spasm and simultaneous spasm in several coronary arteries following the implantation of such stents. The induction of coronary spasm in an artery other than the vessel in which the stent has been positioned, as well as multiple thrombosis located not only in the coronary arteries, supports this theory.[19] The histological findings in patients who died as a result of stent thrombosis show eosinophilic infiltrates and poor intima healing, and the extracted thrombi are seen to contain neutrophil and eosinophil infiltrates.[20] Furthermore, these and other patients receive antiplatelet drugs such as acetylsalicylic acid (ASA) (aspirin) and clopidogrel, which are potentially antigenic.[21]

Physiopathology

Allergens such as foods, insect venom, iodine contrast media or drugs induce mast cell degranulation, resulting in the release locally and into the systemic bloodstream of a number of vasoactive mediators (histamine, leukotrienes, serotonin) and proteases (tryptase, chymase).[22]

Histamine and the leukotrienes are potent coronary vasoconstrictors, while tryptase and chymase activate the metalloproteinases, inducing collagen degradation and erosion of the atheroma plaque–which in turn initiates the coronary event.

Cardiac histamine acts upon four types of receptors, each of which can contribute to the severity of allergic myocardial damage. The H1 receptors mediate coronary vasoconstriction, while the H2 receptors to a lesser degree intervene in coronary relaxation. The interaction between both receptor activities induces a drop in diastolic blood pressure and an increase in pulse pressure. The H3 receptors

Table 1 Etiology of Kounis syndrome.

Environmental exposures	Wasp, bee, ant and jellyfish stings
	Millet
	Poison ivy
	Latex
	Snake and other venom
	Diesel exhaust
	Sarin gas
	Lawn cutting
Diseases and medical conditions	Angioedema
	Bronchial asthma
	Urticaria
	Foods
	Anaphylaxis related to exercise
	Mastocytosis
	Churg-Strauss syndrome
	Drug-eluting coronary stents
	Intracardiac devices
	Takotsubo myocardiopathy
Drugs	
Analgesics	Dipyrone
Anesthetics	Etomidate
Antibiotics	Ampicillin, ampicillin/sulbactam, amoxicillin, amikacin, cefazolin, cefoxitin, cefuroxime, penicillin, vancomycin, ciprofloxacin
Anticholinergic agents	Trimethaphan
NSAIDs	Diclofenac, naproxen, ibuprofen
Antineoplastic drugs	5-Fluorouracil, carboplatin, cisplatin, cyclophosphamide, interferon
Contrast media	Indigotin disulfonate, iohexol, ioxaglate
Corticosteroids	Betamethasone, hydrocortisone
Skin disinfectants	Chlorhexidine, povidone iodine
Muscle relaxants	Cisatracurium, rocuronium
Proton pump inhibitors	Lansoprazole, omeprazole
Thrombolytic agents and anticoagulants	Heparin, streptokinase, urokinase, lepirudin, hirudin, bivalirudin
Others	Allopurinol, enalapril, esmolol, insulin, protamine, iodine, nicotine patches, mesalamine, bupropion, tetanus toxoid

in turn inhibit noradrenalin release, while the H4 receptors regulate mast cell, eosinophil and lymphocyte chemotaxis–producing a change in eosinophil shape and favoring molecular adhesion.[23] Likewise, histamine can activate platelets, enhance the aggregation response of other agonists such as adrenalin or thrombin,[23,24] and reduce tissue factor expression and activity–this enzyme being a key element in the coagulation cascade, favoring the final formation thrombin.

Tissue factors

Chymase converts angiotensin I into angiotensin II, which in turn acts synergically with histamine upon receptors in the cells of the tunica media of the coronary arteries, aggravating coronary spasm.[25]

Not all patients who suffer an allergic reaction develop a coronary event, and it is not clear what determines the occurrence of such events. It has been suggested that there is a limit to the activation of mast cells and the release of mediators, above which coronary spasm and/or plaque rupture takes place. This limit would be intimately associated to the location of the antigen–antibody reaction, the area of exposure, the release of mediators and, of course, the severity of the allergic reaction.[26]

It has been postulated that there are common points between KS and ischemic heart disease not triggered by an allergic reaction. In fact, it has been observed that patients with coronary syndromes not coinciding with allergic reactions have elevated blood and urine inflammatory mediator (histamine, leukotrienes, thromboxanes, interleukin-6 and even tryptase) concentrations compared with healthy individuals.

There is even sufficient evidence to suggest that the inflammatory cells which infiltrate the atheroma plaque (mast cells, macrophages and T lymphocytes) do so before actual plaque erosion occurs, not only as an acute inflammatory response during the coronary event. These data could have future implications for identifying patients at risk or for planning treatment strategies.

Diagnosis

The diagnosis of KS is eminently clinical, and is based on the identification of signs and symptoms suggestive of an acute

Table 2 Clinical and electrocardiographic findings.

Symptoms	Signs	Electrocardiogram
Chest pain	Arterial hypotension	Negative or flat T-wave
Dyspnea	Diaphoresis	ST-segment elevation/descent
Weakness	Paleness	Wide QRS
Malaise	Palpitations	Prolongation of the QT interval
Nausea	Bradycardia	Sinus node tachycardia
Vomiting	Tachycardia	Sinus node bradycardia
Dysphagia	Cardiorespiratory arrest	Nodal rhythm
Syncope		Atrial fibrillation
Pruritus		Extrasystoles
Urticaria		Bigeminism

allergic reaction and a coronary event coinciding in time. The patient presents a coronary syndrome that can manifest as malaise with chest pain of anginal characteristics, and simultaneously also shows symptoms typical of an anaphylactic reaction: hypotension in the context of contact with a known allergen, skin manifestations (rash, urticaria, angioedema), respiratory alterations (dyspnea, wheezing, dysphonia, stridor) and/or digestive disorders (abdominal pain, nausea, vomiting).

Coronary syndrome includes unstable angina with or without evidence of vasospasm and/or acute myocardial infarction, accompanied by electrocardiographic alterations and/or cardiac enzyme elevations. The most frequent symptoms and the electrocardiographic alterations are described in Table 2.

The clinical history is essential for establishing a cause–effect relationship in time with the possible triggering factor. In this sense, and in addition to the usual information, we must explore the possible allergic antecedents of the patient (allergy to latex, fruit, drug substances and situations such as insect stings or the recent use of medications that may have gone unnoticed, such as NSAIDs).

There is no diagnostic test pathognomonic of KS. When the syndrome is suspected, we must do the following:

1. Electrocardiogram (ECG): Although the most frequent ECG finding is ST-segment elevation in the four anterior and inferior leads, the tracing may be normal or show only nonspecific findings. The right coronary artery is the vessel most often affected by vasospasm, though the reason for this is not clear (Table 2).
2. Laboratory tests: These tests on one hand are used to assess cardiac damage and are the tests usually requested in the case of patients with ACS (cardiac enzymes, blood count, cholesterol levels, D-dimer), and on the other hand they are used to evidence a possible allergic reaction (levels of tryptase,[27] histamine, arachidonic acid products, interleukins, tumor necrosis factor (TNF), complement, eosinophilia, total IgE and specific IgE). The guides recommend the determination of tryptase, histamine, complement, eosinophils and total IgE. Normality of these parameters does not rule out the possibility of a prior allergic reaction.

   According to the Spanish Galaxia guide, tryptase concentration is the most useful parameter for diagnosing anaphylaxis, offering a sensitivity of 73% and a specificity of 98%. These percentages moreover increase if the parameter is evaluated on a serial basis. A minimum of three determinations is recommended: on starting drug treatment immediately after the reaction; two hours after symptoms onset; and again after 24 hours. The tryptase levels usually return to normal between 6 and 9 hours after the reaction.

   Serum tryptase is a more practical marker of mast cell activity than plasma histamine. This is because the half-life of histamine is 60 minutes, with a maximum peak 5–10 minutes after the start of the reaction, versus 90 minutes in the case of tryptase–a fact that facilitates use of the latter. Measurement of methylhistamine in 24-hour urine also can be performed.

   The absence of specific IgE antibodies or of total IgE elevation does not discard mast cell degranulation, since in principle degranulation occurs when the allergic reaction is mediated by IgE–and this is not always the case.

   Other inflammatory markers such as the leukotrienes and thromboxanes are unable to differentiate this syndrome from a traditional ischemic event, since they show significant elevations in acute myocardial infarction of non-allergic origin.
3. Echocardiogram: Echocardiography can differentiate the syndrome from other causes of chest pain such as pericarditis or aortic dissection. The echocardiogram reveals segmental contractility alterations in most of the patients; these alterations usually disappear within a few days or weeks, without complications following the acute phase.
4. Arteriography: This technique may be required to evaluate the coronary anatomy, treat vasospasm with intracoronary drugs, or perform angioplasty where indicated. In those patients in which type II KS is suspected, intracoronary ultrasound also should be performed to identify occult coronary disease.
5. Vascular biopsy: This technique reveals mast cell infiltration at the site of spasm, in the ruptured plaque, and also in zones susceptible to atheromatosis.[28] However, the myocardial biopsy findings are typically normal.
6. At discharge it is advisable to refer the patient to the specialist for full allergological evaluation.

Treatment

At present there are no specific clinical practice guides referred to KS, and most of the information on the treatment of this syndrome comes from individual case reports or case series. The indicated management is that specific to ACS and anaphylaxis, with the added complication that the drugs used, while clearly indicated in application to these disorders considered separately, may present contraindications when administered jointly in one same patient. This aspect is particularly relevant in relation to the use of adrenalin. As a result, the treatment of KS merits a series of special considerations, as described below.[29]

Management of acute coronary syndrome (adapted from the guides of the American College of Cardiology and the American Heart Association[30])

While oxygen and vasodilators are indicated in all patients, the usefulness of other drugs such as ASA, clopidogrel, nitroglycerin and beta-blockers should be evaluated taking into account the potential risk of aggravating the anaphylactic reaction.

Acetylsalicylic acid (aspirin)

Aspirin should be administered to all patients with ACS as soon as possible, and dosing should be continued indefinitely unless when contraindicated (level of evidence I, grade of recommendation A). In allergic patients or subjects with important gastrointestinal intolerance, use can be made of clopidogrel.

Aspirin can cause allergic reactions and even anaphylactoid conditions. Indeed, as a result of its mechanism of action, aspirin may even worsen pre-existing anaphylaxis. As a result, its usefulness in KS is not clear, for although it is beneficial in ACS, it could also worsen anaphylaxis. If following due evaluation of the risk-benefit ratio, the decision is made to administer aspirin, treatment reasonably should be provided in the ICU.

In patients with type II SK and allergy to aspirin, we can perform desensitization with this drug.

Nitroglycerin

Nitroglycerin increases myocardial oxygen release, dilates the coronary and peripheral vessels, and lowers preload. Patients with ACS should receive intravenous nitroglycerin in the first 48 hours, in the event of persistent ischemia, heart failure or arterial hypertension (AHT) (level of evidence I, grade of recommendation B).

Nitroglycerin can cause hypotension and tachycardia, which could complicate an anaphylactic reaction—though it seems reasonable and safe to use it in patients who are not hypotensive.

Beta-blockers

These drugs block the effect of the catecholamines upon the cell membrane receptors. Although beta-blockers are useful in coronary syndrome, they can lessen the beneficial effects of adrenalin, which is the treatment of choice in anaphylaxis. In patients with anaphylaxis and hypotension who were previously receiving beta-blockers or who receive such drugs for ACS, use can be made of glucagon.

Calcium channel antagonists

Calcium antagonists are the drugs of choice when the cause of the chest pain is vasospasm, as occurs in unstable angina. They are also a good option if beta-blockers are contraindicated. Since calcium antagonists may prove useful in the treatment of bronchospasm induced by hypersensitivity, they may be regarded as a first line option in the antiischemic treatment of patients with KS.

Morphine

Morphine offers potent analgesic and anxiolytic action. However, opiates such as morphine, codeine and meperidine must be used with caution, since they can give rise to nonspecific mast cell granulation and thus worsen the allergic reaction.

Fentanyl and its derivatives show only limited mast cell activation and may be the option of choice when opiates are required.

Oxygen

Oxygen should be administered to patients with ACS in the presence of saturation values of under 90%, or a risk of hypoxemia. In patients with anaphylactic shock, 100% oxygen should be administered, with ventilatory support if needed. The indication of oxygen therapy is therefore not subject to debate.

Management of anaphylaxis (adapted from the guides of the American College of Allergy, Asthma and Immunology[31])

Adrenalin

Adrenalin is the treatment of choice in anaphylaxis. It is able to prevent and revert bronchospasm and cardiovascular collapse, and moreover must be administered early, because doing so has been shown to improve patient survival.

The administration route recommended by the guides for the treatment of anaphylaxis is the intramuscular route (thigh muscle) at a dose of 0.3–0.5 ml of adrenalin 1:1000 in adults. The dose can be repeated after 20 minutes. On the other hand, in the context of ACS, adrenalin can worsen the ischemia, prolong the QT interval, and induce coronary vasospasm and arrhythmias. Therefore, in patients with KS, the risks may outweigh the benefits, and further studies are needed before any firm recommendation on the use of adrenalin can be established.

Adrenalin is to be avoided in patients with a history of sulfite allergy, since many adrenalin formulations contain sodium metabisulfite.[32]

H1 blockers

H1 receptor blockers are regarded as second line treatment after the administration of adrenalin, which they are unable to substitute in the treatment of anaphylaxis. H1 blockers improve symptoms such as pruritus, rash, urticaria and angioedema. They must be administered slowly, however, since bolus dosing can cause hypotension and impair coronary flow. They therefore are recommended only in hemodynamically stable patients. H1 blockers are advised in KS (dexchlorpheniramine 5 mg, up to a total of 18 mg a day).

H2 blockers

H2 blockers can prevent gastrointestinal bleeding. Their use is recommended, since it seems that the joint administration of H1 and H2 blockers affords better results than treatment only with H1 blockers.

Corticosteroids

Corticosteroids are potent antiinflammatory and immune suppressor drugs that play an important role in allergic reactions, beginning to exert their effects 6 hours after administration, and are useful in preventing biphasic and

prolonged anaphylaxis. Corticosteroids in patients with vasospastic angina and evidence of allergy or symptoms refractory to high vasodilator doses have demonstrated their efficacy in resolving the symptoms.[33,34] Although corticosteroids may slow and impair healing, with thinning of the myocardial wall, their use in KS is possibly safe and adequate—though further studies are needed in this context.

Intravascular volume replacement

In anaphylaxis, up to 40% of the intravascular volume is displaced into the interstitial compartment, causing hypovolemia and hemoconcentration. Volume expansion is therefore important in such cases. However, patients with KS can develop left ventricle dysfunction, and volume expansion may lead to acute lung edema and respiratory failure. Hemodynamic monitorization is thus required, along with echocardiographic assessment of left ventricle function.

Mast cell stabilizers (nedocromil, sodium cromoglycate, ketotifen)

Mast cell activation is the primary mechanism underlying KS, and mast cell stabilizers may alleviate the allergic reaction and reduce thrombotic phenomena. Although their efficacy and potency are questionable, their use can be considered in patients who develop ACS following drug reactions.[35] A recent review published by Ridella et al.[36] reports that most cases have been treated with corticosteroids (76%), H1 blockers (70%), nitroglycerin (47%) and H2 blockers (35%), while adrenalin was only used in 23% of the cases, and ASA in 18%. In the case of atopic patients, tests must be made of the stent components, with desensitization if the results prove positive, and mast cell stabilizers should be provided, associated to corticosteroids. Some cases may require immune suppressors.

Prognosis

Although some studies have found the prognosis to be better in type I KS, in both types the prognosis depends on the magnitude of the initial allergic reaction, the patient sensitivity, comorbidity, location of the antigen–antibody reaction, the concentration of the allergen, and its penetration route.[37]

The prognosis is very good beyond the acute phase, during which the patient may develop lung edema, arrhythmias and very rarely thrombi—though death is very rare. Long-term follow-up confirms the good prognosis, with a low incidence of heart failure, and should include an echocardiogram four weeks after patient discharge, to confirm the normalization of left ventricle function.[38]

Full resolution of the contractility alterations within a matter of weeks is characteristic of the syndrome, and other possible diagnoses must be discarded if such resolution does not occur.

Although no recurrences have been reported, repeat exposure to the allergen could cause a new episode.

Conclusions

KS is underdiagnosed, and further studies are needed to better understand its epidemiology, clinical characteristics and diagnosis, as well as to better define the opportune preventive and therapeutic measures. Treatment of the allergic reaction may suffice in type I syndrome, though in type II KS it is moreover obligatory to treat the ACS through dilatation of the coronary arteries. Vasodilator drugs, including nitrates and calcium antagonists, must be regarded as first line options in this case.

Conflicts of interest

Eduardo Palencia-Herrejon has received economical compensation for teaching and consulting activities from Astra Zeneca, Baxter, Edwards, Lilly, Pfizer and GSK.

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